CASE REPORTS

SIMULTANEOUS TREATMENT OF HYPERTENSION AND OPIATE WITHDRAWAL USING AN α_2-ADRENERGIC AGONIST

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This report describes the treatment of a Viet Nam veteran with an α_2-adrenergic agonist (clonidine) for hypertension which had an additional beneficial effect of allowing withdrawal in ten days from 20 mg of methadone a day with minimal withdrawal symptoms.

Clonidine hydrochloride is an antihypertensive agent whose mechanism of action appears to be central α_2-adrenergic stimulation in the nucleus tractus solitarus and the dorsal motor nucleus of the vagus.[1] In addition, it appears that clonidine also stimulates the α_2-adrenergic receptors located in the substantiae gelatinosae of the spinal cord and trigeminal nucleus, the locus coeruleus, the dorsal medial thalamus, and others. Interestingly, it is hypothesized that the clinical manifestations of abrupt opiate withdrawal in addicted patients is due to a norepinephrine hyperactivity in the locus coeruleus, and clonidine has been shown to depress this activity.[2] Thus, clonidine has been used as a "safe and effective nonopiate treatment for opiate withdrawal which suppresses the symptoms and signs of opiate withdrawal, as well as the affective changes associated with opiate withdrawal, such as anxiety, irritability and anger."[3] This report describes the treatment of a black male Viet Nam veteran who presented with hypertension and a desire to be withdrawn from a daily maintenance dose of 20 mg of methadone.

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CASE REPORT

A 35-year-old patient presented to the Psychiatric Emergency Service of Jackson Park Hospital[4,5] complaining of problems with family, gangs, multiple drug and alcohol abuse, violent impulsive behavior, and suicidal ideation. As a result, the patient was admitted to the inpatient psychiatric unit for treatment of his problems. Current history revealed that the patient had been drinking approximately 1 1/2 pints of gin or wine daily for about six months. He also reported he had been injecting two to three bags of heroin a day for the past nine days, in addition to "T's" (pentazocine hydrochloride [Talwin]) and "blues" (tripelennamine [Pyribenzamine]). Further, he reported self-injecting cocaine about two days prior to admission and was also taking 10 mg of diazepam orally four times a day. He had been in a methadone maintenance program for two days prior to admission and had been maintained on 20 mg of methadone per day before signing out. He also indicated that he had dropped out of another methadone outpatient program about two weeks prior to admission after having been on this program for approximately 2 1/2 weeks. Finally, the patient reported taking 250 mg of methyldopa twice a day for hypertension.

Past history revealed that the patient had been addicted since he was wounded in Viet Nam—resulting in a right nephrectomy and subsequent hypertension—in 1966. He was using "hard" drugs until 1973 when he began a methadone maintenance program and remained in that program for

four years. Thereafter, he was incarcerated for one year where he abused pentazocine and diazepam. After his release, he began using pentazocine hydrochloride and tripelennamine, but returned to heroin for 1½ years. One year prior to admission he entered another methadone program and was detoxified over a 21-day period. He had used opiate substances and drank heavily during the past year until about 4½ weeks prior to admission when he again began a methadone maintenance program (as previously noted). Physical examination was essentially normal with the exception of multiple recent "tracks" along the patient's arms, and scars on his right flank, abdominal midline, and right inguinal area due to surgery received in 1966. His blood pressure was 120/70 (as he had been taking his 250 mg methyldopa twice a day regularly prior to admission). Routine laboratory tests (venereal disease reaction level, chemistry profile, complete blood count, sickle cell screening, urinalysis, and chest x-ray) were essentially negative with the exception of slight elevations of LDH, alkaline phosphatase, and GGT-peptidase, which likely indicated a mild pathologic condition of the liver due to the patient's heavy alcohol abuse.

On admission, the patient was placed on 250 mg of methyldopa twice a day. After he began to manifest withdrawal symptoms of lacrimination, rhinorrhea, yawning, and perspiration, 20 mg of methadone was administered daily at 10 AM. After some initial confrontations and threats about what he would not tolerate, the patient realized that his physician "did not play" and some grounds for mutual respect were established. At this point the patient decided he would cooperate with the treatment of his transient situational stress reaction and in addition he wished to be taken off methadone while in the hospital. As a result, four days after his admission he was switched from 250 mg of methyldopa twice a day to 0.1 mg of clonidine three times a day for his hypertension. He was also placed on 50 mg of chloropromazine at bedtime for complaints of difficulty in sleeping. On the fifth day of hospitalization his methadone was reduced to 15 mg daily and on the following day his daily medication was raised to 100 mg of chloropromazine at bedtime and 0.2 mg of clonidine three times a day. On the seventh day the methadone reduced to 10 mg daily. The patient continued to complain of difficulty in sleeping and reported he felt a bit on edge. As a result he was given 25 mg of chloropromazine three times a day. His only other complaint was that he had developed a cold two days prior. On the tenth day of his stay, the clonidine was increased to 0.2 mg four times a day and the methadone was reduced to 5 mg daily the following day. He began to report that the chloropromazine made him drowsy during the day, so he was switched to 10 mg of loxapine three times a day. He voiced no further complaints except for the cold, which caused a nonproductive cough. On the 13th day of hospitalization the loxapine was reduced to 10 mg twice a day, because of his complaint of still feeling drowsy during the day. This was also the last day he received methadone. (Thus, the withdrawal from 20 mg to 0 mg of methadone a day required ten days.) On the 15th day of hospitalization (second day without methadone) the patient continued to deny any withdrawal symptoms but was still complaining about his cough and reported that his cold was causing him to perspire a bit. As his blood pressure began to rise (from 120/70 to 150/90) he was placed on 40 mg of furosemide and potassium supplements daily. On the 18th day of hospitalization (5th day without methadone) the patient continued to report an absence of withdrawal symptoms and went on to report that even his cough had improved.

After the initial hostility on the first day of admission, the staff reported that the patient had been cooperative, in good spirits, and actively involved in many activities. This evaluation of his behavior continued throughout the detoxification process and well after the patient was no longer on methadone. As a result, the following day he received a 24-hour pass to prepare for discharge. The day before discharge (20th day of hospitalization) the patient began to talk in greater detail about his life—how tragic it had been because of his being wounded and his subsequent addiction to drugs and how going to jail had cost him his wife, four children, home, car, etc. He talked with some tremulousness in his voice about his deeper sense of sadness, emptiness, and despair. It was pointed out to him that his gregarious, sociable, charming behavior was in fact a mask to hide his pain. He agreed and further stated he likely took out the anger and frustration caused from his pain on himself, thus his life style and drug use. He was given an aftercare appointment and discharged the following morning with an admonishment to conquer

his problems at their roots (ie, his inner emptiness and chronic low grade depression) rather than by trying to hide from them by using "interpersonal masks" and drugs. The patient was given two-week supplies of clonidine (0.2 mg, four times a day), furosemide (40 mg daily), daily potassium supplement, chloropromazine (50 mg, one or two to be taken at bedtime if needed), and loxapine (10 mg, to be taken twice a day if needed) until he was able to attend his outpatient doctor's appointment. He also received a warning about the possible untoward effects of abrupt clonidine withdrawal (rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headaches and—while rare and not clearly proven—hypertensive encephalopathy and death).

DISCUSSION

The use of methadone as a withdrawal agent for opiates has brought the benefits of having an oral route of administration, a longer duration of action, and a less intense withdrawal pattern than those seen with morphine or heroin. The drawbacks of using methadone for detoxification from opiates are due to minimal or no withdrawal symptoms until the third day, and then a peak intensity on the sixth day after complete withdrawal of the methadone. This is in distinct contrast to the signs of withdrawal from morphine or heroin, which begin in eight hours and reach their peak intensity in 36 to 72 hours. Another shortcoming of detoxification using methadone is that it becomes more difficult when the daily dose reaches 20 to 25 mg per day (it is unclear whether this is due to psychological or physiologic effects) and creates major difficulties for patients withdrawing from methadone maintenance.[6,7]

When it was discovered that there were elevated densities of α_2-adrenergic receptors in several areas of the brain that also showed elevated densities of opiate receptors, it was theorized that the interaction of the enkephalinergic and noradrenergic systems was responsible for the opiate withdrawal syndrome.[8] This led to the use of clonidine in treating the withdrawal symptoms from methadone and substantiated the hypothesis that noradrenergic neuronal hyperactivity was responsible for the opiate withdrawal syndrome in man.[3] It was shown that clonidine produced a tonic inhibitory influence on the noradrenergic cells of the locus coeruleus, causing its withdrawal-suppressing effect.[8] Further, since clonidine does not act at the opiate receptor during the treatment of withdrawal from opiates, it does not carry any component of opiate tolerance due to changes at opiate receptors, thus allowing a chance for the endogenous opioid systems to normalize during clonidine treatment.[9] Accordingly, a major shortcoming of using methadone to detoxify patients with opiate addictions has been resolved.

This is clearly apparent in the case presented. Cessation of methadone maintenance produces complaints of weakness, anorexia, insomnia, abdominal discomfort, headache, sweating, and hot and cold flashes. Vomiting and diarrhea are not prominent and muscle pains are absent. While these symptoms are mild in comparison to heroin or morphine withdrawal syndromes, and have been described as a "mild case of the flu," the distressed behavior of anxiety, irritability, and anger are prominent.[7] The presented patient's major complaint while being withdrawn from methadone was that of insomnia. He denied having any serious withdrawal symptoms; however, it seems likely that what he referred to as a cold that caused him to cough, feel slight malaise, and some minor sweating were in fact withdrawal symptoms. The patient also complained of feeling drowsy and it is difficult to say whether this represented the residual complaints of withdrawal (lethargy and weakness), whether it was due to the chloropromazine given to him to allevaite his insomnia, or whether it was due to the clonidine, which can also cause sedation. Clonidine can cause hypotension in normotensive subjects withdrawn from methadone; however, as the patient had hypertension, clonidine had been prescribed mainly for the effect of lowering his blood pressure to a normal range.

Of interest is the fact that opiate withdrawal is associated with dopaminergic hyperactivity. Although some feel this is not related to the symptoms or symptomatic relief of the withdrawal syndrome,[3] and the blockage of dopamine by using neuroleptics such as chloropromazine has not been shown to be of significant help in narcotic withdrawal,[6] the author's clinical opinion is that there may be some withdrawal symptoms caused by dopaminergic neuronal hyperactivity (possibly insomnia) that can be alleviated by neuroleptics. Dopaminergic neuronal hyperactivity is also a

likely etiologic factor in the schizophrenia syndrome and, in addition to dopaminergic antagonists (such as neuroleptics) being found to reduce schizophrenic symptoms, naloxone (a narcotic antagonist) has been shown to reduce psychopathology in schizophrenic patients. Therefore, just as there is an interaction between the enkephalinergic and dopaminergic systems in narcotic withdrawal, these two systems may also be intimately related in the schizophrenic syndrome. This is supported by the clinical observation that older former heroin addicts often present with a late-developing schizophreniform disorder. Clinically, they remain "interpersonal" but report auditory hallucinations along with a chronic deterioration in function. Thus, they are often misdiagnosed as chronic, undifferentiated schizophrenics who have "burned out."

It should be noted that the patient in the case report was started on clonidine the day before the withdrawal of methadone was begun. This was done to prevent the observed finding that patients receiving clonidine two to three weeks prior to the withdrawal of opiates may develop a tolerance to the clonidine antiwithdrawal syndrome effects. Further, it has been shown that the maximum blood pressure decrease while using clonidine occurs within two to four hours, which correlates with the finding that clonidine has a withdrawal suppressing effect for four to six hours with the peak effect at two hours.[10] The patient noted this phenomena by "internal scanning"[11] while on clonidine three times a day requiring the dosage schedule to be expanded to four times a day (he reported feeling a bit edgy four hours after one of his three times a day doses). Also, while the patient had reported engaging in habitual excessive drinking for six months prior to admission, there was a curious lack of alcohol withdrawal symptoms. This may have been due to the possibility that clonidine may reduce the anxiety, tension, hypertension, and sweating in alcohol withdrawal (as well as other types of withdrawal syndromes) due to the alcohol withdrawal pattern also being a product of noradrenergic neuronal hyperactivity. Finally, "craving"—which narcotic addicts report is an uncanny need for opiates occurring after complete detoxification from narcotics and may last for years in addition to being a possible etiologic factor responsible for ex-addicts often substituting another addiction for narcotics—may be due to a type of neurotransmitter receptor cell supersensitivity similar to the one theorized for tardive dyskinesia that occurs secondary to prolonged blockage of receptor sites.

CONCLUSION

The use of clonidine to treat the patient's hypertension made it possible to successfully withdraw him from methadone because of the concomitant action of clonidine in the nucleus tractus solitarus and dorsal motor nucleus of the vagus (causing the antihypertensive effects) and in the locus coeruleus (causing a withdrawal syndrome suppression effect). It is evident from a review of the literature and the ease with which the patient was withdrawn from 20 mg of methadone per day over a ten day period that the use of α_2-adrenergic agonists such as clonidine may radically alter the treatment of opiate- and methadone-addicted patients. It seems likely that pharmacotherapy will begin to progress from the process of serendipity predominate in the past to a more rational, theory-based process in the future. This will allow for improved treatment of black patients who seek to manage the stress of "survival fatigue" by altering their states of consciousness in harmful ways, such as drug addiction, and pave the way for teaching them more positive ways of stress management.[12]

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ANENCEPHALY: AGENT ORANGE IMPLICATIONS?

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A case of anencephaly is presented and the question of its association with Dioxin ("agent orange") is raised.

Anencephaly is a congenital absence of the membranous skull and cerebral hemispheres due to a defect in closure of the neural tube during the prenatal period. It is evident immediately at birth when the brain stem and basal nuclei are easily recognized at the base of the skull.[1] These infants are either stillborn or die within a few days of birth.

CLINICAL BACKGROUND

A 27-year-old woman, P0010, was referred for ultrasonographic scanning of the uterus to determine the gestational size of the fetus. Her abdomen was noticeably enlarged.

Multiple transverse and longitudinal ultrasonographic scans of the uterus (Figures 1 and 2) revealed an anteriorly placed placenta at the right side of the uterus, polyhydramnios, and the fetal abdomen, thorax and limbs but no signs of a fetal head. Repeat examination revealed similar findings. Amniography using 50 mL of 50 percent Hypaque confirmed the diagnosis of anencephaly (Figure 3). The patient subsequently delivered a stillborn anencephalic fetus.

It is of further clinical interest to note that following this delivery, and prior to April 1981, three other patients also gave birth to anencephalic infants at Queens Hospital Center.

Recent publicity and alarm regarding the use of Dioxin ("agent orange") as a defoliant prompted investigation as to the possible causes for these anomalies.[2] It was revealed, however, that none of these four patients, or their mates, had a history of exposure to agent orange or to other known drugs that may be genetically harmful.

DISCUSSION

Ultrasound scanning of the uterus can demonstrate an absence of the skull in an anencephalic fetus as early as 16 to 18 weeks gestation. It should be performed on any mother who is at risk since in those who have given birth to one anencephalic child there is a 10 percent recurrence risk of closure defects of the neural tube.[1] Elevated α-fetoprotein content of the amniotic fluid, as in the present case may also be helpful in establishing a diagnosis of anencephaly.

A routine roentgen flat plate of the abdomen and pelvis is also useful in establishing this diagnosis. Some difficulty may be encountered, however, because of the concomitant excessive amniotic fluid, and the infraimposition of maternal osseous structures and bowel contents. Transabdominal amniography will clearly demonstrate the absence of the fetal skull (Figure 3).

Agent orange is a herbicide containing equal parts of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid. It was used extensively as a defoliant in the Vietnam conflict, as

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